REMARKS

Claims 44 and 69-73 are pending in the present application.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 44 and 69-73 stand rejected for alleged failure to comply with the written description requirement because the instant specification does not provide verbatim support for oligonucleotides in which a plurality of consecutive α-nucleosides or 4'-thionucleosides linked by charged 3'-5' phosphorous linkages are present. Applicants respectfully request reconsideration because (1) the patent laws do not require verbatim support and (2) those skilled in the art reading the instant specification would readily understand that Applicants were in possession of the claimed subject matter.

It is well established, for example, that the written description requirement does *not* require a patent applicant to provide a verbatim description of all his claimed invention. *Union Oil Co. Of Cal. v. Atl. Richfield Co.*, 208 F.3d 989, 997-1001 (Fed. Cir. 2000). Rather, the test for sufficiency of support in a patent application is whether an applicant's disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citing *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985)).

There can be no genuine dispute that Applicants' instant specification satisfies this standard. The specification, for example, describes oligonucleotides that may be "formed from a ***plurality*** of ***linked nucleosides*** selected from ***α-nucleosides***, β-nucleosides including 2'-deoxy-erythro- pentofuranosyl β-nucleosides, [and] ***4'-thionucleosides***." (specification at page 6, lines 23-26; emphasis added). Thus, the fact that Applicants were in possession of an invention involving a plurality of linked α-nucleosides or 4'-thionucleosides is beyond genuine dispute.

Further support for the claim language is provided by Applicants' disclosure that an oligonucleotide of the present invention may comprise "at least two regions", a first of which

may include "α-nucleosides linked by charged and neutral 3'-5' phosphorous linkages" and/or "4'-thionucleosides linked by charged and neutral 3'-5' phosphorous linkages" (specification at page 6, lines 31-37). This disclosure conveys to those skilled in the art that the inventive oligonucleotides may include a plurality of consecutive α-nucleosides and/or a plurality of consecutive 4'-thionucleosides, which accords with the scope of rejected claims.

When the above-described portions of the instant specification are considered in combination with Example 2A (which discloses an oligonucleotide that includes a region of consecutive α-nucleosides) and Example 7 (which discloses an oligonucleotide that includes a region of consecutive 4'-thionucleosides), it is clear that the instant specification as a whole supports the inclusion of a plurality of consecutive α-nucleosides and/or a plurality of consecutive 4'-thionucleosides.

For the foregoing reasons, Applicants request that the rejection for alleged lack of written description be reconsidered and withdrawn. *In re Alton*, 76 F.3d1168, 1175 (Fed. Cir. 1996) ("if a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.").

Rejection Under 35 U.S.C. § 103(a)

Claims 44 and 69-73 stand rejected for alleged obviousness over the combined teaching of four references, *i.e.,* Uhlmann & Peyman, Chemical Reviews, The American Chemical Society, June 1990, Vol. 90, No. 4, pp. 543-578 ("the Uhlmann reference"), PCT Pub. No. WO/1991/010671 ("the Cook publication"), Secrist et al., J. Med. Chem. 1991, Vol. 34, pp. 2361-2366 ("the Secrist reference"), and U.S. Pat. No. 5,354,656 to Sorge et al. ("the Sorge patent"). Applicants respectfully request reconsideration of this rejection because the proposed combination impermissibly exploits the hindsight provided by Applicants' own disclosure. There is no reason to believe that a person of ordinary skill having knowledge of the references (but not Applicants' disclosure) would have modified the references' teachings in a way that would have produced a claimed invention. In fact, the proposed combination

represents a classic example of using an applicant's own disclosure as a roadmap for piecing together the various teachings of prior art in a way that would produce the claimed invention.

The rejection's principal deficiency is that it is based upon the flawed logic that because the "general benefits" of a wide variety of oligonucleotide modifications were individually known in the art for disparate purposes, it therefore would have been obvious to those of ordinary skill in the art to pick and choose among such modifications to construct an oligonucleotide having the precise combination recited in the instant claims. Indeed, the rejection is not based upon any *particular* findings as to why those of ordinary skill would have: (1) selected the cited references for combination, (2) culled the requisite modifications from the references; and (3) aggregated these modifications in a way that would have produced a claimed invention. The hindsight-induced failings of this approach to the issue of obviousness were noted by the Federal Circuit in its recent decision in *Takeda Chem. Indus. Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. June 28, 2007). As the Federal Circuit noted, obviousness cannot be established based on a combination of references absent "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" 492 F.3d at 1356-57 (citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1731 (2007)). *See also May 3, 2007 Memo from Margaret A. Focarino, Deputy Commissioner for Patent Operations, U.S. Patent Office* ("it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. ") (commenting on *KSR Int'l Co*, 127 S. Ct. 1727 (2007)). Since the outstanding Office Action fails to provide any such reason, the instant rejection for alleged obviousness is improper on its face and should be withdrawn.

That those of ordinary skill would *not* have had any reason to combine the cited references in the manner that the Examiner proposes is clear from the references themselves. The Uhlmann reference generally discusses methods for the synthesis of antisense oligonucleotides, including a substantial number of different, candidate oligonucleotide modifications. In fact, a cursory review of the table of contents of the Uhlmann reference reveals that at least 18 major classes of modifications are discussed (*see* section II B that has five subsections, section II C that has seven subsections, and sections II D, II E, and II F that have two subsections each). Certain of these subsection are further sub-divided, *e.g.*, section

II F 1 having parts (a), (b) and (c). Because the Office Action mentions only one such modification, it mistakenly gives a reader the impression that the Uhlmann reference would have led a person of ordinary skill specifically to select alpha-nucleosides as an oligonucleotide modification when, in fact, the reference's disclosure is not even remotely so focused and suggests a large number of possible choices.

The additional references cited by the Office do not supply the necessary teaching or suggestion to create the claimed combination. The Office similarly misrepresents the context of the Cook reference, which discloses a large number of different oligonucleotide modifications in many different combinations, but includes no teaching or suggestion to make the particular combination of the present invention. The Office cites page 163 of Cook publication for its disclosure in "EXAMPLE 170" (one of a large number of examples in which many different combinations of oligonucleotide modifications are disclosed) of a compound comprising several alpha-nucleosides and several beta-nucleosides (of which no more than four are consecutively linked). However, the Cook publication merely confirms, as was already acknowledged in the present application (*see, e.g.*, page 19, line 37 to page 20, line 13), that those skilled in the art are *capable* of incorporating alpha-nucleosides into antisense oligonucleotides, and provides no affirmative teaching or suggestion as to oligonucleotides comprising two separate regions comprising a plurality of consecutive alpha-nucleosides and at least five consecutive beta-nucleosides, respectively, or that such modifications could be made in order to enhance nuclease resistance. The Cook publication does not place any special emphasis on the oligonucleotide modifications disclosed in EXAMPLE 170 as compared with the broad array of other combinations disclosed in the publication, and there is no other suggestion to choose the claimed combination of features in order to enhance nuclease resistance, or for any other purpose. The Office has therefore improperly disregarded the context in which the material for which the Cook publication is cited appears, and has clearly mislabeled the Cook publication as one which provides something other than a generalized listing of possible oligonucleotide modifications.

The Examiner's reliance upon the Secrist reference is not only flawed for similar reasons, but is also substantively improper. First, the Examiner cites that reference for its

teaching that the incorporation of 4'-thioribonuclosides into DNA molecules "may confer some useful biological activity" (8/22/07 Office Action at page 3), but fails to establish how a person of ordinary skill would have been motivated to produce an oligonucleotide that comprises a combination of a plurality 4'-thioribonuclosides and the other specific elements recited by the instant claims. Second, although the Secrist reference discloses that 4'-thioribonuclosides can bestow resistance to *bacterial* cleavage (which Office Action erroneously equates with enzymatic cleavage) and nucleoside phosphorylase resistance, there is no evidence of record indicating that these properties would have been of interest to those of ordinary skill attempting to develop the claimed compounds. Resistance to bacterial cleavage may be useful in certain circumstances, but those of ordinary skill faced with the problem of enzymatic (nuclease) degradation in cellular environments would not consider this property to be relevant; most cellular environments, except in individuals suffering from infection, do not present the problem of bacterial cleavage. Likewise, phosphorylase resistance merely refers to the resistance of a nucleoside to the addition of a phosphate group, and is not related to the phenomenon of nuclease degradation. Furthermore, the Secrist reference clearly states that the "useful biological activity" upon which the Examiner relies to support combination of the cited references (Office Action at page 3, citing Secrist reference at page 2361, 2nd paragraph) is contingent on an enzymatic process (*i.e.,* phosphorlyation of nucleosides by cellular kinases[1]) that is not relevant to Applicants' claimed invention. Thus, the Examiner's reliance upon the Secrist reference is misplaced.

Finally, the Examiner's characterization of the Sorge patent is factually incorrect. The Examiner contends that the Sorge patent discloses the use of alpha-thio-deoxynucleosides to confer resistance to cleavage at the 3' end of a nucleic acid molecule. The patent, however, only discloses alpha-thio-deoxynucleoside ***triphosphates***, *i.e.,* nucleosides in which the phosphate closest to the nucleoside ring is substituted with a thiol group, which are significantly different from 4'-thionucleosides (*see* Sorge patent at abstract, lines 11-12; col.

---

[1] *See* Secrist reference at page 2361, sentence bridging the first and second columns ("Such metabolically stable nucleosides, ***if they are phosphorylated by cellular kinases*** capable of interfering selectively with DNA synthesis or being incorporated into DNA, ***might have*** useful biological activity") (emphasis added).

11, lines 25-26; col. 12, lines 13-32; col. 16, line 49 & lines 63-64; col. 17, line 10; and, claim 12). The Examiner appears to have simply plugged Applicants' claim language "alpha-thio-deoxynucleoside" into a database search of the published literature, and then failed to take account of the fact that the result of the search – the Sorge patent – discloses a molecule whose only similarity to the subject matter of the instant claims is partially overlapping nomenclature. The Sorge patent does not teach or suggest the use of 4'-thionucleosides, much less the use of a plurality of consecutive 4'-thionucleosides in combination with the other specific oligonucleotide modifications recited by the instant claims.

In sum, the rejection of claims 44 and 69-73 for alleged obviousness lacks evidentiary support and impermissibly exploits the hindsight provided by Applicants' own disclosure. Accordingly, the rejection is improper and should be withdrawn.

Conclusion

The foregoing represents a bona fide attempt to advance the present case to allowance. In view of the preceding, Applicants respectfully request withdrawal of the rejections of the claims, and submit that the pending claims are in condition for allowance. If the Examiner has any questions, the Examiner is invited to call the undersigned at (215) 568-3100.

Date: December 19, 2007.

/Joseph Lucci/
Joseph Lucci
Registration No. 33,307

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439